

John A. Hamilton

UNIVERSITY OF TORONTO MEDICAL JOURNAL



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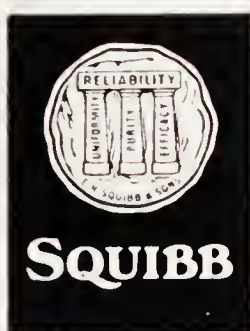
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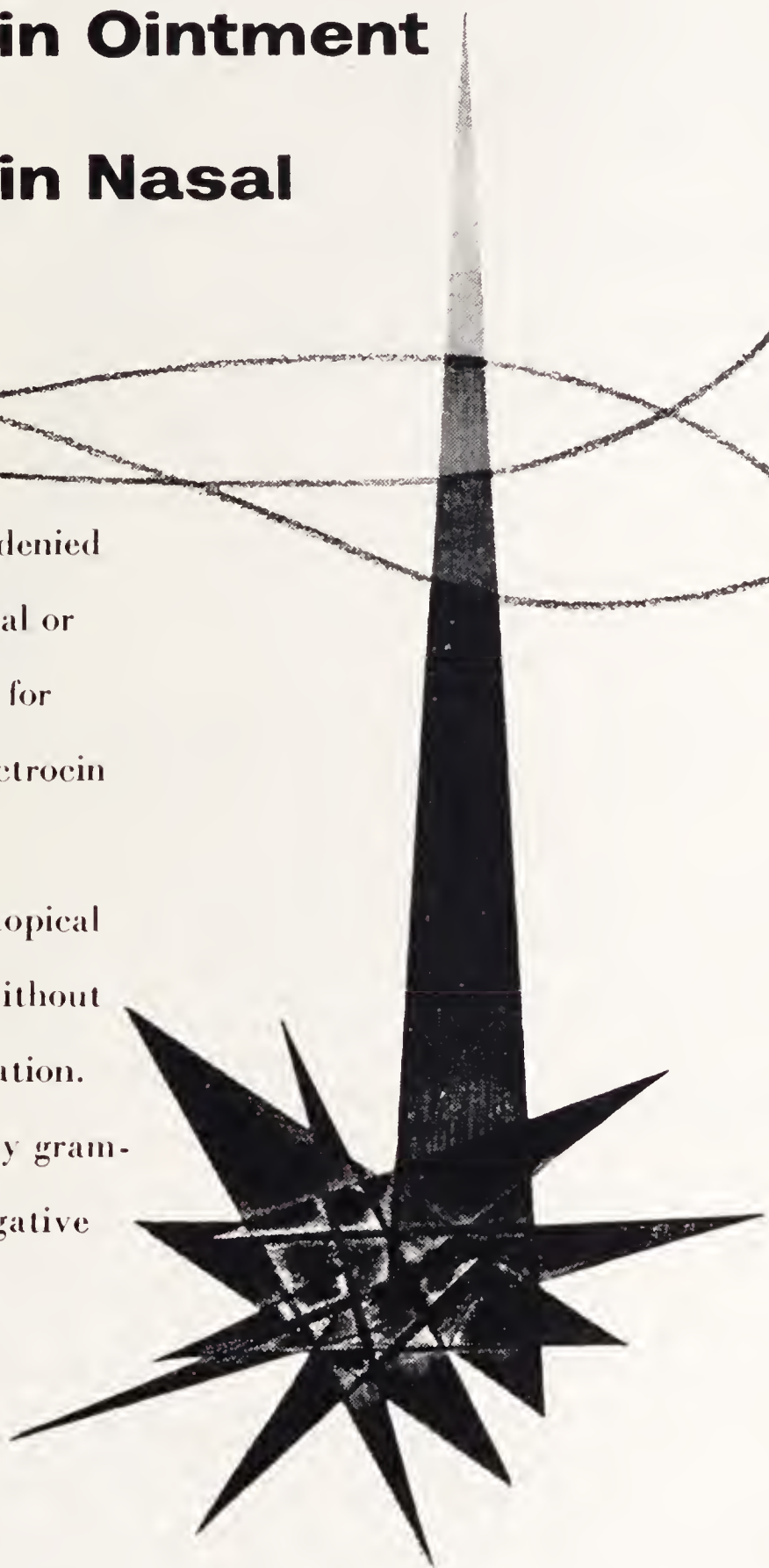
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EDITORIAL

GRADUATION 1956

The great day is approaching. After six years of the grind—listening, reading, watching, waiting, memorizing, forgetting, and occasionally learning—we shall leave the world of classes and exams and emerge as graduates in our field. The change will be miraculous. No longer shall we have to say to the census taker apologetically, “No, I don’t work, I’m a student”. No longer shall we live in the shadow of artificial tests of our ability. We shall cast off the sackcloth of anonymity and overnight be lifted up in the eyes of man to a station of honour, trust, respect, and even awe. We shall be Doctors.

On the surface all these things may be true; in name we shall have changed, we shall have graduated. But are we not fundamentally just the same immediately before as after graduation? As a matter of fact, we are not! With all the fanfare and pride of graduation comes something with which many of us have had little experience before, and which is at that time more important to us than the achievement of graduation itself. This something is responsibility. This is not the responsibility we feel for getting assignments in or writing three histories a week; this is the responsibility which a woman going into labour places upon us, which a man with his first anginal attack entrusts us with, and which every patient we undertake to treat deserves as his undeniable right.

With our entrance into the medical profession we become dedicated to a set of ideals which are inherent in the practice of medicine and which we are obligated to strive toward constantly. These ideals are expressed in the Hippocratic Oath, and similarly in the Declaration of Geneva which was adopted by the General Assembly of the World Medical Association as a pledge on entering the medical profession, and which reads:

“I solemnly pledge myself to consecrate my life to the service of humanity.

I will give to my teachers the respect and gratitude which is their due;

I will practice my profession with conscience and dignity;

The health of my patient will be my first consideration;

I will respect the secrets which are confided in me;

I will maintain by all the means in my power, the honour and the noble traditions of the medical profession;

My colleagues will be my brothers;

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient;

I will maintain the utmost respect for human life, from the time of conception; even under threat, I will not use my medical knowledge contrary to the laws of humanity.

I make these promises solemnly, freely and upon my honour.”

This pledge is not a tenuous, high-sounding collection of platitudes made up by others for the observance of others, but embodies the moral and ethical principles which are the basis of good medical practice. When we disregard, forget or compromise these ideals, we are failing to fulfil our fundamental responsibility as doctors.

B. L.

THE TREATMENT AND PROGNOSIS OF ECLAMPSIA*

M. M. SPIVAK, 5T6

THE treatment of any disease should follow the discovery of its cause and be based on its correction or eradication. Unfortunately, this is not possible in the case of eclampsia, for in spite of continuous investigation, its etiology still remains obscure. It is known generally as the disease of unproven theories. Treatment therefore must be empirical and symptomatic and, as a result, the therapy of eclampsia is as varied as the theories of its origin.

Obviously, it is not possible to discuss in detail this broad and controversial subject in a single paper. Only the following points will be stressed:

1. Prophylaxis.
2. The mechanism of production and treatment of the eclamptic convulsion.
3. Methods of termination of pregnancy.
4. Immediate and ultimate prognosis.

PROPHYLAXIS

Many obstetricians, especially those in Australia, have shown that in good maternity hospital practice, a determined effort to eliminate eclampsia may be completely successful. This has been achieved by providing excellent pre-natal care, consisting of regular visits to clinics or private physicians with urinalysis, weight and blood pressure determinations on each occasion. In this way, the earliest signs and symptoms of pre-eclampsia can be detected and appropriate dietary and medical treatment can be instituted immediately. By the employment of these precautionary measures, and by promptly terminating

pregnancy in those cases which either do not improve or which become progressively worse under treatment, the frequency of eclampsia has been greatly diminished and many lives saved.

A less optimistic view is taken by Eastman, who believes that eclampsia is *not* wholly preventable even with superb treatment. However, the onset of convulsions in a case of pre-eclampsia under observation is a grave development, and represents a grievous failure of pre-natal care.

THE ECLAMPTIC CONVULSION

Once eclampsia has developed measures should first be directed towards controlling the convulsions, because their repetition leads to the deterioration of the patient and may end in her death. When they are controlled, the pregnancy may be terminated (in ante-partum or intra-partum cases) as soon as it is consistent with the patient's safety.

It behoves us therefore to study the mechanism whereby convulsions are produced, and then to describe the steps that may be taken to prevent their recurrence.

MECHANISM OF PRODUCTION

An external stimulus is often the immediate cause of the development of a convulsion. The convulsion occurs because the patient has been sensitized by one of the following factors:

1. A state of nervous hyperexcitability associated with the presence of cerebral edema and the excessive retention of sodium ions.
2. A state of hypertension. The convulsion is usually preceded by a sudden

*From a paper presented before AOA Honour Medical Society.

rise in blood pressure, and is a manifestation of a hypertensive encephalopathy. There is spasm of the central arterioles leading to zones of cerebral anoxia.

3. A predisposition to fits as shown by cerebral dysrhythmia on the E.E.G. If pre-eclampsia occurs in a dysrhythmic individual the likelihood of fits ensuing is much greater than if it occurs in a patient with a normal cerebral pattern.

Based on the above factors, these are the theoretical modes of treatment to prevent convulsions.

Avoidance of Stimuli This was first emphasized by Stroganoff in 1924. However, by itself, it is never very effective and in a busy hospital it is difficult to eradicate noise, and such stimuli as examination of the patient and labour pains cannot be avoided.

The Diminution of the Patient's perception of Stimuli This was also advocated by Stroganoff and it forms the basis of those sedative methods which are still in vogue today.

The Reduction of Cerebral Edema This is the basis for the use of I. V. hypertonic glucose.

The Reduction of Hypertension With a fall in blood pressure, the cerebral arterioles dilate, the ischemic cerebral foci are abolished and the convulsive process ceases.

Most obstetricians use a combination of these modes of therapy to treat their eclamptic patients. However, aside from the specific therapy being used, most hospitals follow the following general principles.

TREATMENT OF THE CONVULSION:

GENERAL PRINCIPLES

1. The patient should be admitted to a dark quiet room with a regulated temperature and be placed on her side without a pillow under her head.

2. The foot of the bed should be elevated to expedite drainage.

3. The patient should never be left alone. Constant nursing care.

4. The following should be available in the room: Oxygen, mouth gag, suction machine, endotracheal tube, and tracheotomy tray.

5. Dentures should be removed if present.

6. Nothing is given by mouth unless the patient is thoroughly conscious, as she may aspirate.

7. Temperature, pulse, respirations, blood pressure, level of consciousness, cyanosis and fetal heart rate should be checked regularly.

8. Once under some specific therapy, a retention catheter should be inserted.

9. The patient should be turned every 2 hours.

SEDATION

Most obstetricians use a combination of sedative drugs in a modified type of Stroganoff regimen (reducing the patient's perception of stimuli). The more popular drugs employed for this purpose have been: *chloroform*, *morphine*, *chloral hydrate*, *paraldehyde*, *sodium amytal*, *sodium luminal*, *pantopon* and *demerol*.

Statistics from leading authorities using these drugs in over 1,000 cases of eclampsia indicate that the best maternal and fetal mortality rates that can be expected are 7.5% and 30% respectively.

Recently Dewar & Morris in England have used *Tribromethanol* (Bromethal, Avertin) on a large series of eclamptics and report a maternal mortality of 4.5%. This drug when given in a rectal drip acts as a powerful anti-convulsant (by lowering the blood and C.S.F. pressures) and is a better sedative than morphine. It acts in 10-15 minutes and its effect lasts for 3-5 hours. Other workers have verified these results.

Mode of treatment	Number of cases	Maternal mortality %	Foetal and neonatal mortality %
Sedation	1071	7.56	29.17
Sedation + Hypotensive (Bromethol)	149	4.03	32.58
Hypotensive (Veratrone)	498	1.81	28.46

FIG. 1.—Comparison of the maternal and foetal mortality resulting from the various types of anti-convulsive therapy used in cases of eclampsia.

Magnesium Sulphate remains one of the most popular drugs used in treating eclampsia. It is a central nervous system depressant and a vasodilator. The drug can be given both intramuscularly and intravenously. Both Eastman & Dieckmann recommend it highly.

O'Donel Browne of the Rotunda Hospital (Dublin) recommends a continuous intravenous drip of *Sodium Pentothal* in 5% glucose as a means of allaying convulsions, and demonstrates favourable results in his series of cases.

More recently *Chlorpromazine* (Largactil) has been introduced into the armamentarium. Although its employment is still in the experimental stage, those workers using it are very enthusiastic. They describe a *hibernation technique*, in which *largactil*, *phenergan*, *demerol*, and *diparkol* are mixed and given intravenously. The patient falls into a deep sleep *from which she can be aroused* and the convulsions cease. Doses may be repeated at regular intervals.

INTRAVENOUS GLUCOSE

Dieckmann states that the proper use of hypertonic solutions of glucose in eclampsia is one of the outstanding accomplishments of modern obstetrics. It

causes hemodilution, reduces intracranial pressure and increases the urine volume. Thus it is particularly valuable if oliguria occurs. However, it must be given fairly rapidly to achieve results: 500–1000 cc. of 20% glucose must be given intravenously in 30–50 minutes. This dose may be repeated 2–3 times daily.

By such administration little or no glucose is found in the urine, but a polyuria results, and once a polyuria has been produced in an eclamptic patient by glucose it usually continues. After intravenous glucose administration, the sodium and chloride in the urine are increased. Since they are electrolytes, they will exert a greater osmotic pressure than glucose and thus will produce a greater diuresis.

In presence of heart failure or pulmonary edema, smaller amounts of 30% and 50% glucose should be used. 5–10% glucose is of value to overcome uncompensated acidosis, to give added protection to the liver, and to supply calories to those in coma over 48 hours.

Some obstetricians recommend only 2000–2500 cc. of intravenous fluid daily, while others state that fluids should be pushed—4000–5000 cc. daily. The latter postulate that the patient, although edematous, is actually dehydrated, and requires this fluid to reduce hemoconcentration and to rehydrate the cells.

HYPOTENSIVE THERAPY

Veratrum Viride This drug was introduced as a treatment for eclampsia by Barker in 1857. Since it had many unpleasant side effects, its popularity waned and the drug was generally discredited.

However in 1940, a purified extract marketed under the name of VERA-TRONE was introduced by Bryant and Fleming of Cincinnati. This preparation was free from toxic side effects, was

rapid in action when given by intramuscular or intravenous injection, and was suitable for repeated administration as well as being harmless to both mother and fetus.

The Cincinnati school combined *Veratrine* with magnesium sulphate and intravenous glucose and claimed the lowest maternal mortality rate for eclampsia—1.5%.

Dieckmann felt that the excellent results obtained by the Cincinnati group for the treatment of eclampsia could not be attributed to the *Veratone* alone, as they used other drugs along with it as well as early termination of pregnancy. However, recently, Stern and Burnett in England have verified the results of the Cincinnati group by using *Veratrine* without any sedation and with very small doses of magnesium sulphate, and report a maternal mortality of 1.8%. They feel that the fits are abolished by lowering the blood pressure, and hence the hypertensive encephalopathic process.

Intramuscular or intravenous injections produce a fall in blood pressure and a slowing of the pulse maximal in 10–15 minutes and lasting for 1–2 hours. Generally, the patient feels only a generalized warmth and flushing after administration. Only after marked overdosage are unpleasant side-effects such as nausea and vomiting produced.

These patients are conscious and co-operative and hence respiratory complications are less likely. They can take liquids and food orally and can complain of any untoward symptoms.

Many other centres are now beginning to use purified *veratrum viride* preparations and all claim excellent results.

Hexamethonium Bromide This drug has been used in some centres with fair results but regulating its dosage is difficult, response to the drug is variable, and severe hypotension may result suddenly with fatal fetal anoxia. Some

authors report that infants born after its use have a paralytic ileus, and others develop a bronchopneumonia. Generally, most authors believe that it should not be used.

Apresoline has been used with fair results.

CONDUCTION ANESTHESIA

Bryce Smith and Williams as well as others believe that in the desperately ill patient who does not respond to treatment by sedation, the use of continuous conduction anesthesia offers a more favourable prognosis for the mother and fetus.

They feel that a caudal block is of little value, and although the blood pressure is controlled most effectively by continuous spinal analgesia, the latter method carries with it the risk of meningitis. They recommend, therefore, a continuous lumbar extradural block which is safer and, for 24 hours, will give almost as good results as a spinal. They also feel that since a high block which is optimal for controlling blood pressure will retard labour, it is best to start a pitocin drip. Improvement is striking and since heavy sedation is unnecessary maternal morbidity is reduced and the fetus offered a better chance of survival. Nevertheless, such treatment presents a disadvantage since it is necessary to provide constant supervision throughout the 24 hours by an anesthetist as well as the obstetrician.

OTHER TREATMENT

1. *Venesection* may be used in an emergency to reduce blood pressure and in the treatment of a complicating pulmonary edema.

2. *Digitalis* is used routinely by Eastman as well as others.

3. *Penicillin* and other antibiotics are given routinely by some authors.

4. *Tracheotomy* should be done on patients with laryngospasm or severe

obstruction to the tracheo-bronchial tree and on those who suffer a cerebral vascular accident.

TERMINATION OF PREGNANCY

Most obstetricians feel that as soon as the patient has been free of either convulsions or coma for at least 8 hours, delivery should be considered, provided her physical condition allows it. She is now no longer suffering from actual eclampsia, but has reverted to a very severe pre-eclampsia. If the cervix is soft and dilated at least 1 cm., the membranes should be ruptured and labour should be expected. If it has not occurred within 6 hours, a pitocin drip should be started.

If the cervix is closed and uneffaced, she should have a Caesarian section preferably done under local, caudal or spinal anaesthesia.

If the cervical dilatation becomes stationary at 6 or more cms. with an engaged head, Dürhssens incisions are indicated.

Some authorities believe that in eclamptic patients who become worse under medicinal therapy, Caesarian section may be indicated as a sort of last resort measure. Eastman believes that this policy is ill advised because:

(a) Some of the worst cases of eclampsia to all appearances go on to recovery without operative interference.

(b) Any major operating trauma such as abdominal delivery may well be the blow which turns the tide to death in these critically ill women.

Menon in India has treated all cases of severe eclampsia in which the cervix is closed and uneffaced and the presenting part unengaged by Caesarian section, and has had to resort to this procedure 25 times in his last 105 cases with only 1 maternal death and a 20% fetal mortality.

He feels that Caesarian section in modern times is not dangerous to the

mother and if it is to give the best result it must be done early and not as a last resort when conservative treatment has failed to control convulsions. Although certain sections might be unnecessary in that the patients might be amenable to persistent conservative treatment, he states that eclampsia is a fickle disease and its course and response to treatment is uncertain. Consequently, he feels justified in doing routine Caesarian section in these cases.

After delivery, the patient should be carried on conservative therapy for 24–36 hours in order to prevent post-partum eclampsia.

PROGNOSIS IN ECLAMPSIA

IMMEDIATE PROGNOSIS

In the U.S.A., the average maternal mortality from eclampsia lies between 10 and 15% and the infant mortality ranges between 35–45%. Fatal eclampsia is $2\frac{1}{2}$ times more frequent among negroes than whites. The prognosis is worse in multiparae and in patients over 35 years of age. This may be due to the fact that many of them have underlying chronic hypertensive vascular disease and hence are predisposed to eclampsia by the pathological changes in their vascular, cardiac, and renal systems.

Those with extreme degrees of oliguria or complete anuria have a graver prognosis as well as those with the following (Eden's criteria):

1. Prolonged coma.
2. Pulse rate over 120.
3. Temperature of 103° or higher.
4. Blood pressure above 200 mm.
5. More than 10 convulsions.
6. 10 gms. or more of albumin in the urine.
7. Absence of edema.

If eclampsia comes on during pregnancy, the maternal prognosis is favourably affected as a rule by the death of the fetus, the convulsions usually ceasing soon afterwards.

The longer the time interval between the first convulsion and delivery, the higher the mortality rate.

Recent statistics indicate that the lowest maternal mortality rate that can be expected by treatment of eclampsia with sedation alone is 7.5%, while the treatment of eclampsia by the use of Veratrine can be expected to give a maternal mortality of 1.5%.

ULTIMATE PROGNOSIS

Recurrence of *toxemia* in future pregnancies occurs in 25–30% of cases.

Recurrence of *eclampsia* in future pregnancies occurs in about 2% of cases.

Outlook for a living infant in future pregnancies is better than 80%.

The prognosis is more favourable if eclampsia occurred in the first pregnancy.

Fetal mortality in subsequent pregnancies is 2 times that normally expected.

Recurrent *toxemia* in subsequent pregnancies is 4–6 times that normally expected.

Recurrent *eclampsia* is 7–32 times that normally expected.

Subsequent hypertension greater than 150/90 occurs in 15% of cases.

There are two opposing schools of thought on the question of pre-eclampsia and eclampsia as a cause of chronic hypertension.

Dieckmann believes that the post-toxic patient who still shows hypertension, proteinuria or impaired renal function 6 months or more after delivery, represents and did represent in her hypertensive pregnancy a case of chronic hypertensive vascular disease or renal vascular disease. He believes that such a patient either had hypertensive disease before pregnancy or a predisposition to it by inheritance or physical and mental instability, and that the pregnancy was the exciting factor. In such patients, the combination of the physical changes

and the emotional stresses of pregnancy result in the onset of hypertension which otherwise would not have appeared for years.

Eastman and Chesley believe that pre-eclampsia and eclampsia represent an acute vascular process in the form of muscle spasm which, if allowed to continue for several weeks or so, results in a permanent structural injury to the vessel wall through anoxia. This injury makes itself manifest by arteriolar fibrosis, consequent hypertension and possible renal vascular damage.

The incidence of permanent hypertension following toxemia parallels the duration of that toxemia and this seems difficult to explain on any basis other than cause and effect.

CONCLUSIONS

Although to-day the incidence of eclampsia has diminished, the disease is still of sufficient importance to merit the examination of new methods of treatment. The statistics of reports covering hundreds of cases indicate that at best the Stroganoff treatment and its modifications will result in a 7.5% maternal mortality. This appears unsatisfactory when more efficacious forms of therapy are available such as purified veratrum viride preparations with a maternal mortality of 1.5%. However, it must be kept in mind that the excellent results reported with some drugs are not due to the drugs alone, but to the experience and skill of the obstetrician using it.

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EPINEPHRINE AND NOREPINEPHRINE

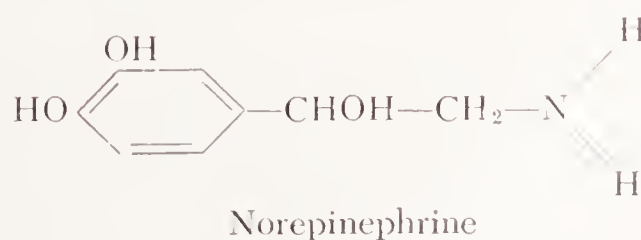
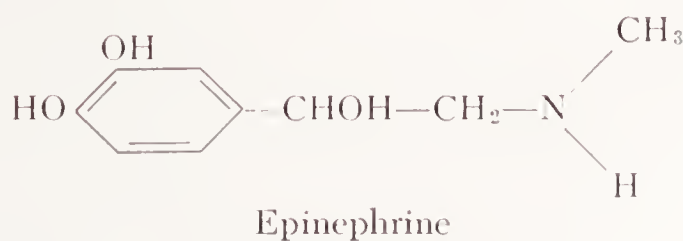
D. C. PRICE, 5T8

ALTHOUGH it is not essential for life, the adrenal medulla, by virtue of its two hormones, epinephrine and norepinephrine, plays an important role in the maintenance of body homeostasis and in the "fight or flight" emergency reaction of Cannon.

PHYSIOLOGY

Following the demonstration by Oliver and Schaefer in 1895 of pressor properties in adrenal medullary extracts, the presence of epinephrine in the tissue was established in 1901. It was not until 1949 that norepinephrine was also definitely established as an active component. By 1921 Cannon and his associates suggested the existence of a

further adrenergic humor, sympathin (sometimes subdivided into the excita-



tory (E) and inhibitory (I) forms), released at post-ganglionic adrenergic nerve endings; present research, how-

ever, indicates sympathin to be a mixture of roughly 20% epinephrine and 80% norepinephrine.

DISTRIBUTION

Chromaffin tissue is the characteristic site of formation of epinephrine and norepinephrine. In man this tissue is found in the adrenal medulla, in the organs of Zuckerkandl, and in the abdominal paraganglia. Also, in man, the two neurohumors are released at all post-ganglionic sympathetic nerve endings except those associated with vasodilation and with the control of the sweat glands and the uterus. The actual proportions of epinephrine and norepinephrine secreted under various conditions of stimulation vary widely. However, the normal adult medullary content of adrenergic substances is estimated to be 14–20% norepinephrine (22 micrograms per gram of tissue) and 80–86% epinephrine (139 micrograms per gram), while at birth the medulla contains 94% norepinephrine (32 micrograms per gram) and the organs of Zuckerkandl virtually 100% norepinephrine (100–175 micrograms per gram).

METABOLISM

It is now accepted that the body forms epinephrine by the methylation of norepinephrine, but the biosynthetic stages preceding this are still much debated. Because of similar embryologic origins of melanoblasts and pheochromocytes, one substantial theory maintains that epinephrine is formed by the conversion of tyrosine to norepinephrine through dopamine. Concerning inactivation of the two hormones, oxidation by amine oxidase is the major pathway. A second significant method is conjugation, with urinary excretion either as an ethereal sulphate or as a glucuronide. The pharmacologically active hormone appears in the urine only when the body content, and consequently the blood level, is abnormally high.

ADEQUATE STIMULATION

I. Endogenous

Norepinephrine functions primarily in body homeostasis, so that internal changes such as a drop in blood pressure will reflexly, through the hypothalamus, stimulate its release. Since epinephrine functions more in emergency or stress reactions, its release will be stimulated both by hypoglycemia and by body stress situations, either emotional or physical (e.g. pain).

II. Exogenous

There are many factors and substances which stimulate adrenergic secretion: direct afferent stimulation, bleeding, asphyxia, and various chemical substances such as caffeine, histamine, carbon monoxide, nicotine, acetylcholine and potassium chloride. Secretion is consistently decreased only by narcosis (e.g. ether or chloroform anesthesia).

TABLE I

	Epinephrine	Norepinephrine
Smooth Muscle:		
G-I walls, bronchioles, bladder wall	relax	relax
G-I sphincters, ureters	excite	excite
Vessels:		
Skin, kidneys	constrict	constrict
Skeletal muscle, liver	dilate	constrict
Coronary	dilate	dilate
Total peripheral resistance	decrease	increase
Heart:		
Rate—isolated	increase	no change
<i>in situ</i>	increase	reflexly decrease
Stroke volume	increase	no change
Blood Pressure:		
Pulmonary	increase	increase
Systolic	increase	increase
Diastolic	no change (decr.)	increase
Cardiac Output	increase	no change (decr.)
Cerebral Blood Flow	increase 20%	decrease 10%
Body Metabolism	increase 30%	no change
Hyperglycemia	present	slight

EFFECTS

In general, except for the effects on the vascular system, the actions of norepinephrine are weaker than those of epinephrine (see Table I).

MODE OF ACTION

Although the two adrenergic neurohumors are believed to act directly upon the effector cells, the reason for an inhibitory action on certain effector organs with an excitatory action on others is unknown. Langley's theory of a chemical receptor substance in the effector cell is often cited as a possible explanation for this divided action.

METHODS OF MEASUREMENT

Epinephrine and norepinephrine can be assayed by colorimetric, fluorimetric or biological methods. The latter two have proved the most sensitive for such small quantities as blood levels, but at present some controversy exists as to their relative accuracies.

CLINICAL ASPECTS

Epinephrine U.S.P. (Adrenaline B.P., Adrenalin, Suprarenin) is most commonly used in the following forms:

- i Aqueous solution 1:1000 of either the hydrochloride or the bitartrate, for injection or direct application.
- ii Aqueous solution 1:100 of the hydrochloride for oral inhalation, using a special nebulizer.
- iii 0.2% in oil of the bitartrate, for injection.
- iv Ophthalmic ointment containing 15 of the bitartrate.

Norepinephrine (Noradrenaline, Arterenol) is available in the naturally-occurring levo-rotatory form as Levarterenol (U.S.P.), made up in 4 ml. ampules which contain 0.2% of the bitartrate, equivalent to 0.1% of the pure base.

CLINICAL APPLICATIONS OF EPINEPHRINE

1. *Control of Hemorrhage.* Owing to its strong vasoconstrictor action in skin and mucous membranes, epinephrine directly applied serves well in arresting capillary bleeding, epistaxis and hematemesis, and in clearing the operating field during procedures on the nose, throat and larynx. 1:2000 to 1:50,000 aqueous solutions are applied either by spray or by cotton or gauze pledget. Suppositories or ointments have been used to treat hemorrhoids. One should never use epinephrine in the treatment of internal bleeding such as pulmonary hemorrhage, as proper vasoconstriction is not likely to occur internally, and the raised blood pressure will only aggravate bleeding.

II. *Shrinkage of Mucous Surfaces.* Relief of nasal congestion in hay fever, coryza and sinusitis is afforded by the vasoconstrictor characteristics of epinephrine. Although solutions in oil have a longer-lasting effect, they are more easily thwarted in their purpose by the cilia of the air passages, and in addition introduce the possible danger of lipid pneumonia. Consequently, a nasal spray of 1:10,000 to 1:5,000 aqueous epinephrine solution is used most frequently, often in conjunction with ephedrine.

III. *Relief of Bronchial Asthma.* The bronchodilator effect of epinephrine is useful in providing relief from asthma, although unwise use of the drug can result in tolerance, and even in psychic dependence. The main route of administration is subcutaneous, with the dose generally 0.2–0.5 ml. of a 1:1000 aqueous solution, this dosage being modified according to the age, severity of attack, and previous therapy of the patient. It is sometimes necessary to continue with similar doses at 15–30 minute intervals until relief is afforded. When thus given subcutaneously, epinephrine is effective for as long as one to two hours.

Intramuscular injection of 0.2–1.5 ml. epinephrine in oil (0.1%) also brings quick relief, lasting in this case from four to twenty-four hours. Consequently it is of great value to chronic asthmatic sufferers for night relief. Again, oral inhalation of an aerosol spray of 1:100 aqueous epinephrine can be used with almost immediate relief, but a proper nebulizer is necessary, and there is greater danger of an accidental overdose. Constant intravenous infusion (generally about 0.1 ml. of 1:1000 epinephrine, appropriately diluted) is used only in certain cases of status asthmaticus, and must be carefully regulated.

IV. *To Combat Allergic Reactions.* Owing to its action as an antagonist of the histamine-like substance released in certain allergic conditions, epinephrine in doses similar to those used in the treatment of asthma is given to relieve attacks of serum sickness and hay fever, and to reduce urticaria and angioneurotic edema.

V. *Stimulation of the Heart.* Epinephrine is of definite value in providing relief from syncopal seizures in Stokes-Adams syndrome, acting by reducing the periods of asystole or bradycardia. In this condition subcutaneous injections of 0.3–0.6 ml. of 1:1000 epinephrine, or in some cases larger intramuscular doses in oil are given as needed. Resuscitation in cardiovascular collapse due to drowning, electrocution or anesthesia (*not* chloroform or cyclopropane) is sometimes effected by slow intravenous infusion of small amounts of the drug (0.05–0.2 ml. of 1:1000 aqueous epinephrine suitably diluted) if the heart sounds are still detectable, or by 0.2–0.3 ml. diluted tenfold and injected directly into the atrium or right jugular vein if the heart sounds are inaudible. However, there is often the real danger of producing fatal ventricular fibrillation by epinephrine injections in instances of cardiac dysfunction. Epinephrine is occasionally of value in acute cardiac failure of central origin, and rarely in cardiac asthma

(provided coronary thrombosis and angina pectoris are absent).

VI. *To Enhance the Action of Local Anesthetics.* Local anesthetics, such as cocaine and procaine, administered in 1:100,000 to 1:20,000 epinephrine solution, gain the advantage of the adrenergic vasoconstrictor activity. Absorption of the anesthetic is greatly slowed, thereby prolonging its action and reducing its effective toxicity to the body. Epinephrine is also sometimes used in small amounts in spinal anesthesia.

VII. *Additional Uses.* Additional clinical applications of epinephrine include the initial emergency treatment of severe hypoglycemia (coma), relief of pruritus in certain types of dermatitis, treatment of syncope due to an abnormally sensitive carotid sinus, relief of glaucoma (1% or 2% epinephrine in ophthalmic ointment is applied locally), and the Ascoli treatment of malaria and malarial splenomegaly.

CLINICAL APPLICATIONS OF NOREPINEPHRINE

Owing to its overall vasoconstrictor activity (unlike epinephrine, which is an overall vasodilator) and the absence of any stimulating effect upon the heart, norepinephrine finds its major application in the treatment of hypotension and certain conditions of shock. It is administered by closely controlled intravenous infusion of approximately 2–4 micrograms of the diluted base per minute, regulated to maintain the blood pressure just below normal. A 4 ml. ampule of the bitartrate is dissolved in one litre of 5% dextrose, or 0.9% saline, which is in turn infused at roughly 1 ml. per minute. Immediacy of therapy is important in shock for maximal vascular response. As might be expected, norepinephrine therapy in hemorrhagic shock is effective only when accompanied by fluid replacement and arrest of the hemorrhage.

A danger in intravenous infusion is that the constant flow of the drug into

a vessel at one point alone, or on the other hand leakage of some pressor substance into the perivascular tissues, will produce sufficiently prolonged local vasoconstriction to result in ischemia and gangrene of distal portions of a limb.

OVERDOSES OF EPINEPHRINE

Epinephrine injudiciously administered can produce fatal ventricular fibrillation by increasing the cardiac muscle sensitivity. In general, clinical overdoses are rare, and inevitably result from a simple mistake of the doctor or nurse in reading the labelled concentration of the drug. Whereas in some patients normal doses can produce anxiety, restlessness, headache, dizziness, pallor, and palpitations, accidental overdoses will produce marked accentuation of these signs and symptoms, as well as sweating and precordial distress. Cerebral hemorrhage due to the sudden rise in blood pressure is a further possible complication.

Recognized overdoses should be followed immediately by an adrenolytic substance, such as piperoxan (15 mgm. intravenously or more in severe cases), or phentolamine (5–10 mgm.). Doses above 2 mgm. epinephrine subcutaneously have been recorded as fatal, and the maximum tolerated dose for human subjects is estimated to be 7–8 mgm. subcutaneously.

CHROMAFFIN TISSUE DYSFUNCTION

I. *Hypofunction*. No clinical entity exists corresponding to decreased epinephrine and norepinephrine formation in the body.

II. *Hyperfunction*. Pheochromocytoma (paraganglioma), a tumor of chromaffin tissue, is quite rare and is seldom malignant, but nevertheless it causes marked symptoms when present owing to increased hormone production. The hormonal content of the tumor is usually in the region of 90% or more norepinephrine, 10% epinephrine. The attacks

resulting from this increase in circulating hormone vary widely in frequency and duration. They have both emotional and physical manifestations, and are met most often clinically as episodes of severe anxiety, trembling, headache, dyspnea, sweating, pallor, severe paroxysmal hypertension, cardiac palpitation, and hyperglycemia. In some instances the hypertension is constant rather than paroxysmal, and many of the above-mentioned episodic signs and symptoms are absent. The most significant diagnostic clinical criteria are a precipitate elevation of both systolic and diastolic blood pressures, and a marked increase in the urinary catechol amine component.

Surgical removal is the only practical therapy for pheochromocytoma. Administration of adrenolytic drugs (phentolamine, piperoxan, or dibenzyl-line) prevents excessive stimulation and release of active hormones into the blood during surgical handling of the tumor. Post-operatively, the precipitate drop in circulating hormone as a result of removal of the active tumor is masked by supplementary intravenous infusion of epinephrine and norepinephrine which is slowly tapered off in the days following operation in order to ease the otherwise sudden effect upon the body.

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COMA

D. H. COWAN, 5T6 and F. D. WALSH, 5T6

COMA is an expression of a disease process in the same manner as cough, vomiting, or dysuria. However, urgent diagnosis is usually imperative and thus it is our intention to discuss some conditions where coma may be the presenting feature.

DEFINITION

Coma is a loss of consciousness with "the absence of any psychologically understandable response to external stimuli or inner need"—i.e. inability to be aroused.

CLASSIFICATION

A complete but concise classification of the multiple causes of coma is not available; therefore, realizing its inadequacy, the following is our classification of the principle causes of coma:

I. INTRACRANIAL

- A. Traumatic (13%)
- B. Circulatory (10%)
 - (a) Arterial
 - (b) Venous
- C. Inflammatory (2.5%)
 - (a) meningitis
 - (b) abscess
 - (c) encephalitis
- D. Neoplastic
- E. Post-Epileptic (2.5%)
- F. Heat-Stroke

II. METABOLIC

- A. Diabetic Coma
- B. Hypoglycemic Coma
- C. Uremic Coma (3%)
- D. Hepatic Coma
- E. Acute Adrenal Insufficiency
- F. Toxemia of Pregnancy
- G. Fulminating Infections (1.5%)

III. POISONS

- A. Alcohol (59%)
- B. Barbiturates
- C. Opiates (3%)
- D. Carbon Monoxide

IV. CARDIO-VASCULAR (1.5%)

V. RESPIRATORY

I. INTRACRANIAL

A. Traumatic

Coma due to trauma may be instantaneous from immediate effects of injury (concussion, contusion or laceration) or delayed with deterioration of consciousness after a lucid or relatively lucid interval.

The history, if available, and signs such as injury to the head, bleeding and/or spinal fluid leakage from the nose or ears, or blood behind an intact ear-drum, are all valuable aids in diagnosis. It should be remembered that trauma may cause coma, or may result from coma—e.g. fall following cerebrovascular accident.

Where coma occurs following a lucid interval the following complications should be kept in mind:

1. Hemorrhage:

(a) Extradural hematoma from middle meningeal arterial bleeding. In this case, early diagnosis is life-saving. Suggestive are the signs of cerebral compression (a falling pulse rate, rising blood pressure and stertorous breathing) and localizing signs (dilating or fixed ipsilateral pupil, motor and reflex disturbances).

(b) Subdural hematoma, acute or chronic. The former occurs after a short lucid interval, while the latter may appear months after the injury. Again,

focal signs and those of increased intracranial pressure are important. It should be noted that 24–48 hours generally is required before papilledema is seen in cases of increased intracranial pressure. It is present in approximately 50% of the chronic type.

2. *Massive cerebral edema.* Diagnosis is by exclusion of the above by trephination.

3. *Post-traumatic meningitis.* Diagnosis is by lumbar puncture.

4. *Pneumocephalus.* This is to be suspected particularly in cases where fractures enter air sinuses.

B. Circulatory

In the middle-age group coma always suggests a cerebro-vascular accident. Signs of unilateral paralysis are common except when the brain stem is involved—e.g. pontine hemorrhage where quadriplegia is a feature.

1. Arterial:

(a) Thrombosis. The onset is slow and gradual compared with hemorrhage or embolism. Generally, occlusion of the middle cerebral and basilar arteries produces coma.

(b) Intra-cerebral hemorrhage. The onset is sudden with almost immediate loss of consciousness. Blood may be found in the cerebro-spinal fluid.

(c) Embolism. The onset is also sudden and in the early stages may be difficult to differentiate from hemorrhage. The source of the embolus should be detected.

(d) Subarachnoid hemorrhage. There is generally an early intense occipital headache associated with a stiff neck. Gross blood is found in the C.S.F. In a young person the most common cause of spontaneous subarachnoid hemorrhage is from an arterio-venous malformation. As the age increases aneurysms become a more frequent cause.

occur in any condition of increased coagulability of blood (trauma, post-

2. Venous:

Intracranial venous thrombosis may partum, severe cachexia), of increased viscosity or of injury to the vessel wall.

C. Inflammatory

1. *Meningitis:* A history of fever, headache, stiff neck and subacute onset of coma should always suggest this condition. A lumbar puncture is mandatory to establish the diagnosis and to differentiate the etiological organism.

2. *Brain Abscess:* This is suspected in any space occupying lesion. Evidence of a primary focus of infection is very suggestive. The usual sites are accessory nasal sinuses, middle ear, mastoid and lung. The encapsulated abscesses tend to give a subnormal temperature and a slow pulse rate, whereas the unencapsulated and subdural variety tend to give a hectic swinging fever. If the meninges are involved the signs of meningitis are superimposed.

3. *Encephalitis:* The findings are similar (but less striking in proportion) to those described for meningitis.

D. Neoplasm

Rarely, coma may be the presenting sign. If present its cause usually is acute obstructive hydrocephalus, tentorial or foraminal herniation, or hemorrhage into the tumor.

E. Post-Epileptic Coma

A past history of seizures or history of convulsions immediately preceding the comatose state are important diagnostic aids. Additional helpful signs are a bitten tongue and incontinence.

F. Heat Stroke

This very rare condition is characterized by a fever of 105°F. or more, with the unusual combination of a rising temperature and a hot dry skin.

II. METABOLIC

A. Diabetic Coma

The patient may or may not be a known diabetic. The signs include deep, rapid 'Kussmaul' respirations, the fruity smell of acetone on the breath, a florid dry skin, soft eyeballs, decreased blood pressure and a weak rapid pulse rate. A 'quiet' coma is present without convulsions. Laboratory findings reveal glycosuria, acetonuria, hyperglycemia and a lowered carbon dioxide combining power.

B. Hypoglycemic Coma

This diagnosis is entertained in a known diabetic on insulin therapy. As opposed to diabetic coma, convulsions, a pale, moist skin, full rapid pulse rate, normal respiratory rate and overactive reflexes are features. The second urine specimen is negative for sugar and the blood sugar is low.

C. Uremic Coma

The gradual onset of coma is usual, generally as a terminal event. Convulsions and muscular twitchings may precede the coma. The breath may have a urinous odor, and a pericardial friction rub may be present. The pasty type of pallor is striking. Proteinuria, low urinary specific gravity, and an elevated blood urea nitrogen are the significant laboratory findings.

D. Hepatic Coma

This is a very rare and sometimes very mysterious cause of coma. Signs of liver disease (ascites, hepatomegaly or small cirrhotic liver, telangiectasia, jaundice, liver palms) may be present, but any or all may be absent. Diagnosis is confirmed by abnormal liver function tests and elevated blood ammonia levels.

E. Acute Adrenal Insufficiency

This condition may occur superimposed on chronic adrenal insufficiency

or may be primary from partial or complete destruction of adrenal tissue by infection (especially meningococcal septicemia), hemorrhage or surgery. Clinically, it is characterized by the signs of peripheral vascular collapse and coma.

F. Toxemia of Pregnancy

In any pregnant woman in the late second or third trimester or in the early puerperium who presents in coma, eclampsia should be suspected. Convulsions may or may not have preceded its onset and twitchings, restlessness, and extreme maniacal disturbances may occur in coma. Edema, hypertension and albuminuria are diagnostic features.

G. Fulminating Infections

Any overwhelming infection may cause coma—fulminating septicemias, enteric fevers, severe exanthemata, and tropical diseases.

III. POISONS

Obviously, there are innumerable exogenous toxins which may cause coma. Only the more common will be discussed.

A. Alcohol

The most common cause of coma results from acute alcoholic intoxication with its well known manifestations. Rarely is this coma so deep that the loss of pupillary and corneal reflexes occurs although such is more apparent with excess methanol ingestion. In the latter, coma is frequently of delayed onset, often with associated optic atrophy (blindness) and acidosis.

It should be remembered that associated or resultant conditions (infections, metabolic disturbances, trauma) are prone to occur in alcoholics and thus the state of inebriation may mask a more serious underlying cause of coma.

B. Barbiturates

The frequency with which alcohol and barbiturates are ingested together must not be forgotten. Lateralizing signs are not a usual feature, but may occur rarely and thus such signs do not automatically exclude barbiturate poisoning. Diagnosis rests on history, the exclusion of other causes, and blood and urine findings of barbiturate levels, if laboratory facilities are available.

C. Opiates

The following signs are suggestive: pin-point pupils, very slow respirations (as slow as 1–2/min.), cyanosis, subnormal temperature, and needle marks on the arms and legs.

D. Carbon Monoxide

This is characterized by a cherry red discoloration of the skin and mucus membranes. The history of the situation is diagnostic.

IV. CARDIO-VASCULAR

The cardiac status of every comatose patient should be assessed as such may be primarily responsible for, or secondarily involved in the comatose state. Acute myocardial insufficiency (e.g. myocardial infarction), arrhythmias (e.g. complete heart block) and hypertension (hypertensive encephalopathy) may cause coma.

Hypertensive encephalopathy may occur in primary or secondary hypertension. Besides coma, distinctive features include papilledema, focal signs and convulsions, all of which tend to be of a transient nature.

Most disturbances of hemodynamics—e.g. hypersensitive carotid sinus—tend to give a transient unconsciousness which would have to be considered when the patient is first seen.

V. RESPIRATORY

Anoxic anoxia may also contribute primarily or secondarily to coma. Aspi-

ration should be considered particularly in alcoholics and epileptics, who may aspirate vomitus while coming out of coma. It should be stressed that an obstructed airway is frequently the cause of deepening coma in a patient already unconscious for some other reason.

THE CLINICAL APPROACH TO THE COMATOSE PATIENT

In the approach to the problem of coma, one should have an organized plan of procedure, modified of course, by the findings as the examination proceeds. An outline of such a clinical approach is therefore presented:

1. *Simple therapeutic procedures.* Primarily, simple therapeutic procedures must be observed e.g. maintaining a clear airway and stopping obvious hemorrhage.

2. *History.* As in any diagnostic problem, the history is of paramount importance. Of necessity, it frequently must be obtained from relatives, friends or bystanders. Any information, no matter how meagre, may furnish the key to the entire problem. Diabetics and epileptics often carry cards signifying the fact.

3. *General Appearance.*

- (a) Age.

Age is also of primary importance. Under 40 years of age, diseases such as epilepsy and infection are common; amongst cerebro-vascular causes, spontaneous subarachnoid hemorrhage is frequent from rupture of a congenital or mycotic aneurysm, or embolus from a fibrillating heart. In older patients, metabolic disorders, cardio-vascular disease, cerebro-vascular accidents and tumors of the brain occur more frequently.

- (b) Signs of Trauma.

There may be obvious signs of trauma such as lacerations or bleeding from the ears, nose or mouth.

(c) *Facies, Position and Attitude.*

The cheek on the paralysed side tends to balloon out on expiration and the face is drawn to the normal side. Paralysis may be hinted at by lack of movement of one or more extremities. The patient with barbiturate intoxication often merely seems to be in a quiet sleep, from which, however, he cannot be aroused.

(d) *Inspection of the Skin.*

The cherry red discoloration of carbon monoxide poisoning, the cyanosis of anoxemia, the hyperemia of the face and conjunctivae in alcoholism, the pallor of severe blood loss, the muddy-grey pallor of uremia, and the jaundice of hepatic disease are some of the more notable cutaneous manifestations.

(e) *The Character of the Respirations.*

Rapid, shallow breathing occurs in severe infections and in heat stroke, while deep, rapid breathing indicates central respiratory depression from barbiturates, opiates or anoxemia, and slow, stertorous or periodic (Cheyne-Stokes) respirations indicate more severe brain stem damage.

(f) *The Odor of the Breath.*

This may be characteristic in diabetic coma, alcoholic intoxication, uremia or hepatic coma.

4. *Head*(a) *Scalp.*

Signs of trauma to the scalp that may not be obvious on cursory observation should be sought for carefully.

(b) *Eyes.*

Eye signs may be helpful, particularly in the early stages of a cerebro-vascular accident: on forcibly opening the eyelids, the eyes, and occasionally the head, may deviate away from the side of the lesion, due to a focus of irritability in the frontal lobe. When hemiplegia supervenes, the eyes tend to be directed toward the side of the lesion. This is known as conjugate deviation of the eyes.

Symmetrical pupillary dilatation is common, particularly in alcoholism and barbiturate poisoning, while unilateral dilatation suggests a focal intracranial lesion. Symmetrical pinpoint constriction suggests opiate poisoning in the hypopyrexia patient, or pontine hemorrhage when associated with hyperpyrexia.

The corneal reflex may be absent unilaterally with focal neurological lesions, or bilaterally if the patient is in deep coma.

Eyeball tension is reduced in states of dehydration, as in diabetic acidosis.

Examination of the fundi may give evidence of diabetes, uremia, generalized cardio-vascular disease or increased intracranial pressure. Optic atrophy may be noted.

(b) *Ears, Nose and Throat.*

One should not fail to use the auroscope to examine the ear-drums. The nasal passages may contain blood-clot. The position of the uvula should be noted and the palatal reflex tested.

5. *Neck.* If the head cannot be flexed on the chest, signs of meningeal irritation exist and suggest either meningitis or subarachnoid hemorrhage. The presence of jugular venous distension and tracheal shift should be tested for.

6. *Temperature.* The body temperature (axillary or rectal) may be helpful. Hyperpyrexia suggests intracerebral hemorrhage (particularly pontine), meningitis or heatstroke. Subnormal temperatures are seen in acute poisoning, some expanding intracranial lesions and, of course, in primary hypothermia from exposure to cold.

7. *Chest and Heart.* Complete pulmonary and cardiac assessment is essential. The character of the pulse and the pulse rate should be noted: the rate is slow in cases of increased intracranial pressure, and complete heart block. An excessively rapid rate may indicate an ectopic rhythm or infection.

The blood pressure should be noted. Hypotensive levels occur in peripheral vascular failure which may result from hemorrhage, myocardial infarction, adrenal insufficiency, barbiturate and alcoholic intoxication, and diabetic acidosis. An increasing hypertension, particularly with a falling pulse rate, is indicative of increasing intracranial pressure.

8. *Abdominal Examination.* One should not overlook this part of the examination; it requires little time to pinch the skin to get an idea of the state of hydration, to test for the abdominal reflexes, to feel for organs or masses, and to test for the cremasteric reflex in the male.

9. *Back and Extremities.* Possible vertebral injuries contraindicate manipulation of the patient. Differences in muscle tone may be noted. One should test the plantar response and try to elicit the deep tendon reflexes.

10. *Neurological Examination.* This has already been completed in the regional examination of the patient. Repeated examination, however, is required to detect changing signs, primarily the development of a Babinski response or other abnormal reflexes. In neurological lesions, the muscles on the affected side tend to be hypotonic in the early stages. Frequently the corneal reflex is absent on the affected side only.

11. *Urinalysis.* Glycosuria is usually demonstrated in diabetic coma but also is sometimes found in cerebral hemorrhage, meningitis, and the first specimen from a hypoglycemic patient. Acetonuria is also frequent in diabetic acidosis but is also found in starvation. Similarly, the urine should be tested for albumin and occasionally, for urobilinogen.

12. *Blood Studies.* The more important examinations of the blood in comatose patients are those for sugar, carbon dioxide combining power and blood urea nitrogen. The clinical picture may de-

termine the specific test required, but frequently, all must be performed. In suspected infection, blood for culture should be taken before antibiotic therapy is instituted.

13. *X-rays.* With a mere suspicion of trauma, X-rays of the skull are indicated, but generally may be delayed until immediate therapeutic measures are undertaken. A negative skull plate does not necessarily imply that trauma is not the underlying cause of coma. Evidence of an expanding intracranial lesion may be confirmed indirectly by skull films in that a shift of the pineal gland (if calcified) may be demonstrable. Occasionally X-rays of the sinuses and mastoids may be advised.

14. *Other Tests.* Gastric lavage is occasionally indicated in poisoning. Lumbar puncture is frequently indicated in unexplained coma, but should not be undertaken if there is any suspicion of a space-occupying intracranial lesion. Electrocardiograms and chest X-rays are occasionally helpful.

SUMMARY

Coma is to be treated as a *sign of a disease process*. A fairly complete, but not unwieldy *classification* of the possible causes of coma should be kept in mind, coupled with a *knowledge of the clinical and laboratory manifestations* of the disturbances included in the classification. *The clinical approach to the comatose patient* is our attempt to present a logical and orderly attack on the problem, and to point out signs that may be particularly significant.

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THE SURGICAL TREATMENT OF BONE AND JOINT TUBERCULOSIS*

P. M. WATSON, 5T6

THE NATURE AND PATHOLOGY OF THE DISEASE

TUBERCULOSIS of bone and joints is a systemic infection by the tubercle bacillus in which the bone and joint involvement is the result of a bacteremia produced by activity in a focus elsewhere, this systemic spread occurring at any time in the course of the primary or secondary infection, or during reactivation. About half the cases of tuberculosis of the bone or joint have radiologically evident pulmonary lesions^{1, 2} one third of them have renal tuberculosis, and one quarter have multiple bone lesions.³

The pathology is that of tuberculosis elsewhere: tubercles, granulation, and cavitation with bone resorption. Bone lesions, most common in children, are usually in the vascular areas of the skeleton, such as the cancellous bone of the vertebral bodies, and the ends of long bones, often in the epiphysis. The joint may be involved either by direct spread from the bone lesion eroding through the articular cartilage, or by primary infection of the synovium, more frequent in adults. The involved synovium thickens greatly and grows over the articular surface, eroding it by

vascularization. The articular cartilage is always involved secondarily, but once destroyed, does not regenerate, leaving a crippled joint which tends to remain infected and eventually to fuse. Intervertebral discs, being relatively avascular, are involved secondarily to adjacent vertebral body infection. In decreasing order of frequency lesions are found in the spine, hip, knee, ankle, sacroiliac joints, shoulders, elbows, fingers, and toes. Abscesses, joint effusions, and sinuses tend to form locally, and if secondarily infected are particularly devastating.

DIAGNOSIS

The diagnosis may be suggested by clinical and x-ray findings, such as a painful deforming arthritis, mild but progressive in nature, with marked muscle wasting, and x-ray evidence of cavities, bone porosity, narrowed disc or joint space, joint surface irregularities, abscess shadows, and abnormal calcifications. A Mantoux skin test should not be omitted. The diagnosis, however, cannot be definitely established without the identification of the tubercle bacillus itself on smear or culture of joint fluid, pus, or tissue, or histological evidence of the typical pathology by biopsy (e.g. of synovium)—otherwise there will be a 25% error in diagnosis.⁴

*From a paper read before AOA Honour Medical Society, February 13th, 1956.

A search must be made in every case for other foci of infection by complete history and physical examination, chest and skeletal x-ray survey, urinalysis, and routine urine and sputum culture and guinea pig inoculation.

GENERAL THERAPY

The general management of the patient is designed to help him conquer his systemic infection by means of rest and chemotherapy. As this is still a prolonged and trying method, it is best carried out in a sanatorium where optimum rest of body and mind, good nourishment, supervision, and education may be achieved. The recommended course of chemotherapy is for a minimum of twelve months with 1 Gm. Streptomycin intramuscularly twice a week, 10 Gm. PAS orally daily, and 300 mg. Isoniazid orally daily.

Before any active local therapy is begun the patient should be in control of his infection. He should feel well, have no fever, no other active foci, x-rays should show stabilization or healing of the lesion, and the sedimentation rate, hemoglobin, and white count should be favourable.⁵ This may take three to six months of general treatment, but such improvement may occur in the local lesion by that time that no operative treatment may be needed.

LOCAL THERAPY

A. BASIC PRINCIPLES

The basic principles of local therapy are two: rest by immobilization, and removal of diseased tissue. Resting the part involved is perhaps the most important single factor in treatment, and has long been known to promote speedier healing and recovery. The best way to achieve this rest is by complete immobilization, perhaps through fusing the joint. Removal of diseased tissue in part or in entirety will aid greatly in combatting the infection.

B. ESTABLISHED PROCEDURES

(1) *To Remove Diseased Tissue*

(a) Aspiration of joints and abscesses is done for diagnosis or if the patient is not responding to chemotherapy.

(b) Incision and drainage of abscesses and sinuses has been made feasible since penicillin has allayed the fear of secondary infection. This is used for persistent lesions.

(c) Amputation and joint excision was the only surgical cure for joint lesions for years, done as early as 1762, and is still used in certain circumstances:

(d) Sequestrectomy is seldom needed now.

(e) Curetting, cutting out, or excavating the bone lesion was and still is the treatment of choice for lesions not involving joints.⁶

(f) Synovectomy, or removal of infected synovium is of disputed value except for diagnosis.⁴

(2) *To Immobilize the Part*

(a) Conservative immobilization such as by traction, frames, braces, splints, and casts, was found in the past to be inadequate in nearly all cases. Joint movement was still possible, healing was slow and doubtful, infection persisted, joint destruction progressed till the joint was useless, and future flare up and systemic spread were almost inevitable.

(b) Therapeutic joint fusion was therefore resorted to, for it truly immobilizes the joint, facilitates or produces solid bony ankylosis, and minimizes future reactivation. It was first done in 1911 by R. A. Hibbs on the spine, and was soon tried on other tuberculous joints with such great success that since then it has been the treatment of choice for joint tuberculosis. The conservative methods of immobilization are still used

initially pre-operatively and post-operatively along with bed rest and chemotherapy for variable periods.

The basic aim of fusion is to attain continuity of healthy bone across the joint, either without disturbing the joint itself—the external fusion, or by removing the diseased bone and fusing right through the joint itself—the internal fusion. The spine is fused externally by uniting the spinous processes by bony bridges. With proper fusion and post-operative care, the patient is usually able to return to a relatively normal life in one to three years. The results of various investigations reported about 1930 show approximately 65% of external spinal fusions to have a stable comfortable spine, and about 90% of hip and knee fusions to be successful⁴—a remarkable improvement on older techniques.

C. RECENT DEVELOPMENTS

In view of the success of chemotherapy today, we must re-evaluate our established treatment methods. Do all tuberculous joints need fusion? Can spinal tuberculosis be dealt with more effectively another way? Recent investigation into these matters has been inconclusive as yet because of limited number of cases and short follow up periods.

The vertebral body and disc disease has been attacked by some surgeons in a new way by an antero-lateral approach directly down to the lesion, with curetting out of the diseased tissue, and then fusion of the vertebral bodies by bone chips or grafts. This internal spinal fusion method is reported by Wilkinson of England to give a stable comfortable spine in 78% of his 65 cases.⁷

Fusion of a tuberculous joint, according to Dr. A. DeForest Smith of New York,⁴ is no longer indicated if the articular surfaces are not involved. He reports six cases in which no articular

cartilage destruction was demonstrated, which were treated by removal of as much diseased synovium as possible, and by curetting out of any bone lesions. In the few years of follow up all but two have had full range of movement and no recurrence of disease. Four similar cases are reported by Dougherty and Sherman⁸ in which bone and synovial disease without articular destruction healed completely without synovectomy, but with curetting of the bone lesions, conservative immobilization for three to six months, and chemotherapy. No recurrence or limited movement existed in three to six years.

It is the opinion of Mercer of Edinburgh⁹ and of at least one authority in Toronto that with minimal involvement of the articular surface, joint mobility should be maintained though it may be limited in range and need future fusion owing to continuing disease or osteoarthritis. Whether this is valid must await the verification of time and further experiments.

Joints which show marked destruction may now fuse spontaneously in a short time by the aid of chemotherapy, thus obviating the need of operation.

SUMMARY

Consideration has been given to:

- nature and pathology of the disease
- diagnosis
- general therapy
- local therapy: principles, procedures, recent developments.

CONCLUSIONS

1. Every case of bone or joint tuberculosis should receive general systemic treatment of rest and chemotherapy, and conservative immobilization of the involved part for three to six months at least before operative intervention.

2. Tuberculosis of bone responds best to curetting of the local lesion even when it approximates a joint.

3. With tuberculosis of the spine, fusion is probably still the safest and most effective treatment, vertebral body fusion perhaps being the most successful type.

4. Tuberculosis of other joints depends in its treatment upon the stage of progression:

(a) without articular surface involvement fusion is not indicated.

(b) with minimal articular surface involvement the decision to fuse may be postponed in hope of maintaining joint function.

(c) with moderate to advanced joint destruction therapeutic fusion is indicated if spontaneous fusion is not imminent.

ACKNOWLEDGMENT

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THE COMPLICATIONS OF BONE AND JOINT TUBERCULOSIS*

W. H. KERR, 5T6

TUBERCULOSIS of bone and joints is almost invariably secondary; it is but a local manifestation of a general disease. As a rule, the bone is invaded first with subsequent spread to the joint, but occasionally the spread is in the opposite direction. Thus, tuberculosis of both bone and joints are complications in themselves of disease elsewhere in the body. The complications of the disease in bone and joints may arise from the disease itself, or from the treatment of the disease. The latter group, due mainly to the prolonged bed rest, will be merely mentioned: they include phlebothrombosis, pulmonary embolism, hypostatic pneumonia, urinary retention,

urinary calculi, osteoporosis, postural hypotension, bed sores, and constipation. The former group, due to the disease process itself, will now be discussed in some detail.

I. ABSCESS FORMATION

Almost every case of bone and joint tuberculosis is associated sooner or later with an abscess—rarely is this complication lacking. Clinically, it is a useful diagnostic feature because it can be detected radiologically and can be aspirated for demonstration of the tubercle bacillus by bacteriological methods.

Pathology. The abscess arises from the rupture of a subperiosteal abscess into the surrounding soft tissue and consists of a central mass of caseous debris with

*From a paper read before A.O.A. Honour Medical Society February 13th, 1956.

a limiting wall of granulation tissue. At any stage an abscess may become stationary and later be absorbed. Occasionally it appears early and grows rapidly, in which case the disease is usually an acutely destructive one. The more usual history is that the swelling slowly increases in size, and under the influence of tension and gravity follows the lines of least resistance towards the surface of the body. Its course may thus be directed by fascial planes, muscle sheaths, nerves or vessels.

Since the cold abscess is most characteristically seen in Pott's disease, where it is the commonest complication, we shall review its various courses according to its anatomical sites.

—In the cervical region, the path is determined by the attachments of the cervical fascia, so that the abscess may produce a retropharyngeal lesion, may enter the mouth or one of the visceral compartments, or may appear posteriorly.

—In the thoracic region, the abscess is usually small and frequently remains in close contact with the spine; however, if it is large, it may extend anteriorly into the posterior mediastinum, posteriorly into the vertebral canal and to the back, laterally into the pleural space or along the intercostal nerves and vessels, or downwards to act as a lumbar abscess.

—In the lumbar region, the abscesses tend to become larger and travel more. They often enter the psoas sheath to form the familiar psoas abscess which may track to the groin, or rarely even to the ankle. Other routes are occasionally followed.

The tuberculous abscess can be harmful both from the toxemia it produces and from its pressure on vital structures such as the spinal cord; it may be further

threatening on account of prospective rupture and the danger of secondary sepsis. Accordingly to Watson-Jones, pus under pressure has a very harmful effect on bone, and thus sound healing of diseased bone seldom occurs in its presence.

Treatment:

- (a) Expectancy: Jones & Lovett estimate that 70% of tuberculous abscesses are absorbed by the body if left alone. The absorption is said not to be detrimental to the patient; indeed Rollier claims that the presence of the cold abscess has an immunizing effect upon the patient.
- (b) Medical Treatment: This consists of expectancy with systemic anti-tuberculous drugs. The results of this have been discouraging.
- (c) Surgical Treatment: This is indicated where there is pressure on vital parts or skin tension, but it is dangerous to leave a cold abscess alone until the overlying skin has become adherent and reddened since secondary infection is then very frequent and rapid joint disintegration, wasting, and amyloid disease follow. The surgical treatment consists of aspiration or incision.

Tuberculous abscesses can often be eliminated by closed aspiration of the pus through healthy tissue, followed by injection of streptomycin with or without isoniazid before withdrawing the needle. However, aspiration cannot be done satisfactorily until the pus is very close to the surface and unless it is very fluid.

If aspiration is contra-indicated or unsuccessful, most authorities do not hesitate to incise and drain under cover of general and local antibiotic therapy. Incision with primary closure is the procedure recommended.

It should be recognized at the begin-

ning of treatment that the residual abscess which no longer has an active focus pouring material into it is more amenable to treatment than the abscess which is continually receiving reinforcement from some focus or active lesion.

II. SINUS FORMATION

When an abscess continues activity the pressure within it increases as more material is added to it. It therefore tends to extend or point in the direction of least resistance. If the abscess discharges on a free surface, a sinus is formed.

Treatment:

- (a) Prophylactic Treatment: Every effort should be made to cause abscesses to heal in order to prevent sinus formation and secondary infection.
- (b) Medical Treatment: Chemotherapy employed locally and generally usually achieves these aims, and even long-standing sinuses will now heal in a few months. However, some feel that chemotherapy alone is a short-sighted policy.
- (c) Operative Treatment: Surgical excision, in addition, is sometimes required if the walls of the sinus tract are very thick, or if there is associated sequestration of bone. The abscess which supplies the sinus tracts must be exposed and drained, or the sinuses will re-open.

III. SECONDARY INFECTION

Secondary infection of an abscess cavity converting a "cold" into a "hot" abscess, or of a draining sinus, is a very feared complication which is difficult to cure and may ultimately be fatal from general toxemia in some cases, but more often from amyloid disease.

Treatment:

- (a) Prophylactic Treatment: This is stressed in the presence of a sinus with danger of secondary infection.

(b) Medical Treatment: Local and general anti-tuberculous drugs and antibiotics which are indicated from culture and sensitivity tests of the discharging material are used.

(c) Operative Treatment: Excision and open drainage under cover of chemotherapy are employed.

IV. DISSEMINATION

This is one of the feared and often fatal complications of tuberculosis anywhere in the body. To-day, with new drugs, it is less so. The risk of general dissemination was considered a strong deterrent to adventurous surgery in the past, that is, to a direct attack on a focus of tuberculous disease. This possible complication may now be less important since the introduction of antibiotics; in fact, some claim that dissemination is rare, if it occurs at all, post-operatively.

V. FAILURE TO RESPOND TO THERAPY

Occasionally, a patient fails to respond to treatment, or the local lesion alone will persist despite improvement in general health. Month after month, X-rays will reveal further bone destruction taking place; there is no sign of arrest of the destruction, and still less of recalcification.

Treatment: Treatment consists of radical excision of all infected parts with subsequent pseudoarthrosis or amputation, as arthrodesis is impractical with too extensive disease. Amputation operative treatment is adopted as a last resort in extreme cases. The probable indications are constitutional disturbances as a result of amyloid disease, cachexia, or the steady advance of the local process, particularly with mixed infection and sinus formation.

VI. SPINAL CORD INVOLVEMENT IN POTT'S DISEASE

Paraplegia arises as a complication of Pott's disease in approximately 10% of

cases, with 80% of these having involvement of the thoracic region.

Etiology:

Edema of the cord can produce a transient paraplegia due to altered circulation in the cord in the region of the lesion without gross compression. It generally appears as a cause in the early and most active stage of the disease.

Compression of the cord can occur from an abscess, granuloma, sequestrum, pathological fracture-dislocation, or from an extreme kyphosis.

Clinically, the cases can be divided into early and late, each with a different treatment and prognosis. The early cases are associated with primary activity of the spinal lesion, while the late cases appear after the disease has apparently been arrested, and are due to unsound healing and the gradual development of deformity.

Treatment:

- (a) Conservative Treatment: Immobilization of the back in a frame or bed along with fixation and traction is indicated in cases of partial motor paralysis without any sensory or sphincter disturbances. In early and mild cases, especially in children, this is sufficient, but in adults operation must be seriously considered. Of course, if there is direct evidence of compression, a more radical approach is indicated.
- (b) Operative Treatment: This is indicated if the paralysis is long-standing, or severe with sensory and sphincter disturbances, or if there is evidence of compression. The choice of operation lies among the following:
 - (1) Costotransversectomy—to evacuate the abscess.
 - (2) Laminectomy—to enlarge the spinal canal and give the cord more space.

- (3) Posterior spinal fusion, which is indicated after the relief of symptoms, is employed to restore stability in the spine and to provide strong, permanent immobilization of the whole of the diseased segment. In mid and lower thoracic disease, it stops the grinding effect of respiration which causes daily addition of debris to the abscess.

In summary, operative decompression of the cord by costotransversectomy and the evacuation of a tense paravertebral abscess, or, less often, by laminectomy, can be a procedure of the utmost value provided that the operation is carried out in association with uninterrupted and adequate immobilization of the spine before, during, and for 3–4 months after the operation.

The prognosis varies with the intensity and duration of the paralysis. Treatment with the hope of complete cure must be carried out within 6 months of the onset, and preferably within 1–2 months. Deep motor paralysis with associated sensory and sphincter disturbances carries with it a poor prognosis; nevertheless, it must be treated.

VII. DEFORMITY

Deformity is a very common complication of tuberculosis of bone and joints. Abnormal joint positions are primarily due to muscle spasm, usually in the direction of more flexion. Later on, organization and fibrous adhesions cause fibrous ankylosis which may become converted into cartilaginous or bony ankylosis, making the deformity more permanent.

Treatment will be discussed in relation to the most commonly involved joints.

- (a) Deformity in the Spine: The aims here are to prevent or minimize the length and degree of primary

kyphosis, and to develop compensatory curves close above and below the kyphus.

Conservative treatment is indicated in the active stage of the disease and consists mainly of recumbency with immobilization of the spine in the neutral position or in full extension. The various forms of splintage include the Bradford frame, the Whitman frame, the Thomas double frame, and plaster shells, all of which allow gradual correction of the deformity. Traction in these splintages is also available, and is often desired in relieving the pain and muscle spasm by separating the diseased and irritated articular surfaces. In the ambulatory phase, a plaster jacket or Thomas brace may be employed.

Operative treatment may be employed in the arrested stage, usually about 3 months after a favourable general response. Surgery on the spine in children is of less value than in adults, and is rarely done. The various operations include central curettage, which involves the curetting of the diseased tissue in the vertebral bodies followed by the filling of any cavities with cancellous bone chips, and posterior spinal fusion, which may be carried out using bone chips, tibial bone grafts, or an H-graft for short synostosis between two vertebrae.

(b) Deformity in the Hip: The deformity includes adduction, flexion, medial rotation, and eventually shortening which is the worst and most intractable deformity, and is due to destruction by the disease and premature closure of the epiphysis.

Conservative treatment is indicated in the active stage as for the spine, and consists of complete recumbency, traction to overcome muscle spasm and pain, and then immobilization in a plaster spica or a Thomas splint with Buck's

extension apparatus. The traction overcomes muscle spasm, relieves pain, prevents ankylosis, and allows gradual improvement of position so that a mobile joint may be obtained; this is more probable to-day with the new anti-tuberculous drugs.

Operative treatment consists of the following forms: (1) primary operations to hasten fusion and shorten convalescence; these include extra- and intra-articular arthrodesis (2) secondary operations to correct old adduction-flexion deformity; these include various forms of osteotomies.

In the ambulatory phase, a Thomas walking calibre can be employed. (c) Other Deformities: In the knee, conservative methods may be tried, especially in children, but in adults an early joint excision to obtain a firm bony ankylosis in slight flexion is the surer and quicker method of cure, and is strongly recommended.

In the shoulder and elbow, excision gives admirable results with free motion.

CONCLUSION

It is to be hoped that these complications may be preventable in the near future by the use of anti-tuberculous drugs; even now, the incidence and significance of the complications have been greatly reduced.

ACKNOWLEDGMENT

The author wishes to thank Dr. F. P. Dewar for his assistance in the preparation of this paper.

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ABSTRACTS

Use of Female Sex Hormone Therapy in Pregnant Diabetic Patients: Priscilla White, Luke Gillespie, and Lloyd Sexton. *Am. J. of Obstet. and Gynecology* 71: 57, 1956.

Dr. White believes that the problem of fetal and maternal accidents in controlled diabetic pregnant women is due to an imbalance of female sex hormones—low levels of serum estrogen, low levels of progesterone and high levels of chorionic gonadotrophins.

The authors claim (1) that this imbalance occurs in abnormal pregnancies in diabetic patients, (2) that it predicts or precedes the complications of pregnancy, (3) that it can be corrected by the administration of female sex hormones, (4) that such correction is followed by improved fetal survival provided other parts of the management of pregnancy and diabetes are observed, and (5) that the imbalance occurs more often and to a greater degree as the evidence of maternal vascular damage increases.

Dr. White divides her diabetic patients into six groups to separate benign from malignant forms of diabetes and to separate patients with vascular disease from those without vascular disease.

The authors give evidence supporting the above five points. The results are compared with the obstetrical diabetic program of the British Medical Research Council which confirms the first three points. The fourth point, that correction alters survival, was certainly not confirmed. Cases with retinopathy were excluded and therefore the correlation with vascular damage was not reported and would fit only into the first three groups. The fetal survival in treated and untreated cases after the 28th week was 70% and 68% respectively

in the British group, but the corresponding survival in the author's treated group which showed no retinopathy was 91%. They attribute this discrepancy to the type of therapy employed, the quantity used, the route of administration, and finally to the British Council's rigid program irrespective of class, clinical or chemical course. The most important cause of high fetal mortality for mild diabetic patients was the lack of individual and constant care and attention. The authors used the parenteral route instead of the oral route as used by the British. The dose of female sex hormone varied, the progressively more severe classes receiving a higher dose schedule.

Other side effects of estrogen therapy were noted. One was that patients with severe retinitis ended their pregnancies with no progression of the retinopathy, and occasionally the eyes appeared to be in better condition at the end of the pregnancy than they were at the beginning. In a significant number of patients, some six months after delivery, severe insulin hypoglycemia occurred and it was necessary for these patients to reduce their insulin requirement, therefore suggesting that the estrogens might cause islet cell hypertrophy and hyperplasia.

The authors' total treatment consisted of seven parts: (1) classification of parents, (2) chemical control of diabetes, (3) female sex hormone therapy (4) correction of any hydramnios or edema, (5) early timing of delivery, (6) special care of infant in post-natal period, (7) yearly observation of offspring of the diabetic mother for evidence of diabetes. Female sex hormone therapy, therefore, is but one-seventh of their entire program and the other six parts cannot be ignored. In the experience of the authors, female sex hormone therapy

when added to the six other principles of management appeared to give greater fetal and maternal protection.

L. CHAIKOF.

Treatment of Hepatic Coma with L-Glutamic Acid: McDermott, W. V. Jr., Wareham, J., Riddell, A. G. *New Eng. J. Med.* 253: 25, 1955.

To clarify the existing confusion regarding the value of l-glutamic acid in the treatment of encephalopathy in patients with disease of the liver and portal circulation, the authors have analyzed their 28 cases in 3 groups based on the pathogenesis of the elevated blood ammonia found in these patients:

I. Patients in terminal hepatic decompensation in which the elevated blood ammonia represents only one facet of a complex metabolic derangement not precipitated by any known exogenous factors—acute spontaneous encephalopathy.

II. Patients with compensated liver disease subjected to an excessive nitrogenous load (high protein diet, gastrointestinal hemorrhage, administration of ammonium chloride as a diuretic)—acute exogenous encephalopathy. In this group, ammonia intoxication is the main biochemical upset responsible for the neurological picture.

III. Patients with liver disease who evidenced a chronic confused state without any rapid progression to coma—chronic encephalopathy. (This group was maintained on a relatively low protein diet throughout the period of treatment, but this alone was insufficient to maintain a normal clinical and biochemical state).

Response to therapy was judged by the fall in blood ammonia (removed by glutamic acid to form glutamine) and improvement in neurological status. Their results showed that l-glutamic acid was most effective in groups II and III,

where the encephalopathy was due to a reversible ammonia intoxication. Patients in group I responded poorly to the drug in spite of a transient fall in blood ammonia. This is to be expected when we consider that ammonia intoxication in these patients is only one of the many facets associated with liver decompensation, and cannot be controlled more than temporarily unless we could visualize a restoration of relatively normal liver function.

The authors conclude by emphasizing the importance of distinguishing between spontaneous and exogenous hepatic coma, the latter referring primarily to the syndrome of ammonia intoxication which is amenable to treatment with l-glutamic acid.

J. L. NAIMAN.

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Few symptoms—little concern. "The [female] patient seeks medical attention because of... leukorrhea... intense itching, dyspareunia and burning and frequency of urination."⁴ However, when the male patient has an infection, he often considers the signs and symptoms as insignificant and accepts them with little or no concern.⁵

Protect the wife. In preventing re-infection, Trussell states, "Obviously a condom will be the most effective mechanical barrier. Eradication of the parasite in both sexual partners is of course the ideal."¹ Karnaky recommends that the husband wear a con-

dom for four to nine months whenever *Trichomonas vaginalis* is resistant and recurrent.⁶

Prescribe top-grade condoms. In prescribing a condom, be selective and take advantage of Schmid product improvements.

Prescribe protection. To eliminate trichomonads "once and for all," take specific measures to win co-operation of the husband. Otherwise he may re-infect the patient and nullify the good results of the regimen. Any husband or wife in your practice would most likely prefer to hand the druggist your prescription for a condom, rather than to ask for it "in public." This is another instance of diplomacy in medicine to prevent an embarrassing situation. To assure finest quality and earn appreciation for your thoughtfulness, prescribe condoms by name. Prescribe Schmid protection for as long as four to nine months after the wife's infestation has cleared. The protection Schmid condoms afford is the very foundation of re-infection control.

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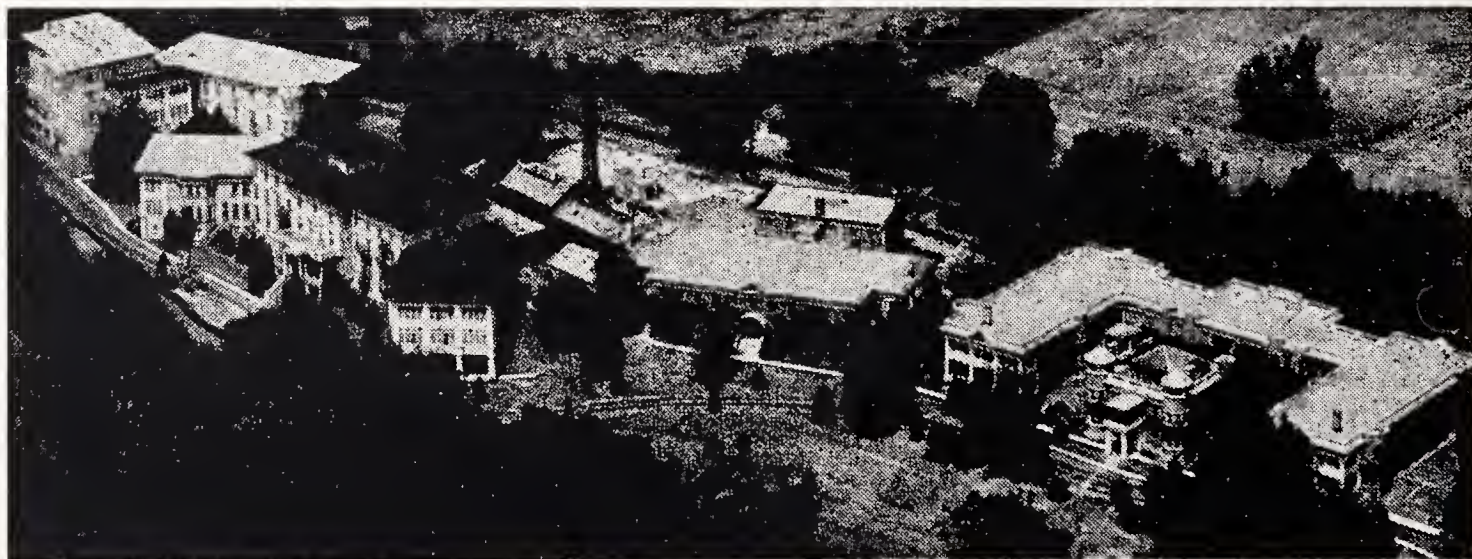
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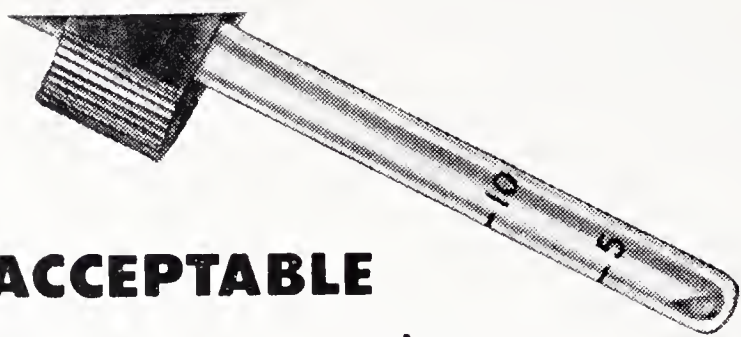
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F R A N K W . H O R N E R L I M I T E D
M O N T R E A L C A N A D A



The most
CONVENIENT, ACCEPTABLE
and **ECONOMICAL** way to administer
MULTIVITAMINS
to **INFANTS** and **CHILDREN**



" **Ostoco** "
DROPS

**WATER-
DISPERSIBLE**

MODES OF ISSUE:

- 8 cc..... 32 days' supply
- 15 cc..... 60 day's supply
- 30 cc..... 120 days' supply

COST PER DAY:

3½ to 4½ cents depending on
size of bottle.

- Each 5 DROP DAILY DOSE (0.25cc.) contains:*
- VITAMIN D..... 1,000 Int. Units
 - VITAMIN A (palmitate).... 2,000 Int. Units
 - VITAMIN C..... 30 mg.
 - VITAMIN B₁ 1 mg.
 - RIBOFLAVIN PHOSPHATE 1 mg.
 - NIACINAMIDE..... 2.5 mg.
 - PYRIDOXINE HCl..... 0.05 mg.
 - SODIUM IODIDE..... 0.04 mg.

*Dose for dose, this "Fross" vitamin
preparation costs the patient less.*

Charles E. Fross & Co.
MONTREAL CANADA